ORIGINAL ARTICLE

Comparative effectiveness of sildenafil for pulmonary hypertension due to left heart disease with HFrEF

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There is no cure for pulmonary hypertension due to left heart disease (PH-LHD), but the rationale for using sildenafil to treat pulmonary arterial hypertension with heart failure with reduced ejection fraction (HFrEF) has been supported by short-term studies. We performed a meta-analysis to evaluate the effectiveness of sildenafil for PH-LHD with HFrEF. A systematic literature search of PubMed, EMBASE and the Cochrane Central Register of Controlled Trials was conducted from inception through October 2014 for randomized trials and for observational studies with control groups, evaluating the effectiveness of sildenafil to treat PH-LHD with HFrEF. Sildenafil therapy decreased pulmonary arterial systolic pressure both at the acute phase and at the 6-month follow-up (weighted mean difference (WMD): -6.03 mm Hg, $P=0.02$; WMD: -11.47 mm Hg, $P<0.00001$, respectively). Sildenafil was found to reduce mean pulmonary artery pressure (WMD: -3 mm Hg, $P=0.0004$) and pulmonary vascular resistance (WMD: -60.0 dynes cm^{-5} , $P=0.01$) at the 3-month follow-up. Oxygen consumption at peak significantly increased to 3.66 $\text{ml min}^{-1} \text{kg}^{-1}$ ($P<0.00001$), 3.36 $\text{ml min}^{-1} \text{kg}^{-1}$ ($P<0.00001$) and 2.60 $\text{ml min}^{-1} \text{kg}^{-1}$ ($P=0.03$) at 3, 6 and 12 months, respectively. There were significant reductions in ventilation to CO_2 production slope of -2.00 , -4.68 and -7.12 at 3, 6 and 12 months, respectively ($P<0.00001$). Sildenafil was superior to placebo regarding left ventricular ejection fraction at the 6-month follow-up (WMD: 4.35 , $P<0.00001$), and it significantly improved quality of life. Sildenafil therapy could effectively improve pulmonary hemodynamics and cardiopulmonary exercise testing measurements of PH-LHD with HFrEF, regardless of acute or chronic treatment.

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INTRODUCTION

Pulmonary hypertension (PH) is a common complication of left heart disease (LHD), frequently occurring as a 'symptom' of the underlying condition.^{1,2} PH associated with LHD is classified as group II PH (postcapillary PH).^{3,4} The current hemodynamic definition of PH-LHD combines a mean pulmonary artery pressure (mPAP) >25 mm Hg, a pulmonary artery wedge pressure >15 mm Hg and a normal or reduced cardiac output (CO).^{3,4} Irrespective of the origin of LHD, the first event leading to PH (isolated postcapillary PH)⁴ is passive backward transmission of filling pressures, mainly driven by left ventricular (LV) diastolic dysfunction.⁵ These purely mechanical components of venous congestion trigger a superimposed component, combining pulmonary vasoconstriction, decreased nitric oxide (NO) availability,⁶ increased endothelin expression, desensitization to natriuretic peptide-induced vasodilation and vascular remodeling.^{2,7} At this stage, mPAP increases further, and this increase seems to occur in excess of elevated pulmonary artery wedge pressure.⁵ Finally, these

changes lead to pulmonary vascular disease (combined postcapillary and precapillary PH),⁴ increased right ventricle (RV) afterload and RV failure.

PH in LHD is most common in patients with heart failure (HF), with preserved or reduced ejection fraction (EF).^{1,2,8} PH-LHD results in more severe symptoms. It causes worse exercise intolerance, exerts a negative impact on outcomes and is often related to disease severity. HF with preserved ejection fraction (HFpEF) is a common cause of PH, associated with worse outcomes than those with HF with reduced ejection fraction (HFrEF).^{2,3,9,10} A multicenter, double-blind, placebo-controlled, parallel study (RELAX) conducted by the Heart Failure Clinical Research Network¹¹ failed to prove that taking sildenafil for 24 weeks could alter exercise capacity or clinical status compared with placebo in patients with HFpEF. Compared with HFpEF, PH-LHD with HFrEF was shown to improve with additional sildenafil therapy, as shown by some single-center, double-blind, placebo-controlled randomized controlled trials (RCTs).^{12–20}

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Compared with pulmonary arterial hypertension (PAH) patients, patients with PH-LHD are more often heterogeneous older women with a history of systemic hypertension,²¹ having most if not all of the features of metabolic syndrome²² and extensive medical histories resulting in complex polypharmacy. There are no validated treatments for PH-LHD, particularly HFpEF. The rationale for using PAH therapies in PH-LHD with HF and HFrEF has been supported by acute or short-term studies using phosphodiesterase type-5 (PDE5) inhibitors (sildenafil).

PDE5 is the principal enzyme responsible for cyclic guanosine monophosphate (cGMP) catabolism in the lungs, and it has been shown in animal models to be upregulated in pulmonary vascular smooth muscle cells under conditions associated with PH.²³ The beneficial effect of sildenafil on pulmonary hemodynamic parameters arises from selective inhibition of isoform 5 (a cGMP-specific PDE) in the pulmonary vasculature.^{24,25}

Most of these studies have consistently reported that there have been improvements in hemodynamic status, exercise capacity and symptoms. However, the methodologies (small sample sizes, single centers, unclear or no randomization processes) have not provided sufficient evidence to support the use of these drugs in the clinical management of patients.

A meta-analysis by Huang *et al.*²⁶ including six RCTs concluded that additional sildenafil treatment was a potential therapeutic method to improve pulmonary exercise capacity and quality of life (QoL) in patients with chronic systolic HF. However, the meta-analysis did not include three RCTs^{16,18,19} and one observational study²⁷ with a control group. It also did not compare the effects of short- and long-term therapy separately.

We sought to improve upon the previous meta-analysis by addressing these issues. By pooling the available literature, we sought to assess the impact of sildenafil for PH-LHD with HFrEF, including hemodynamics, exercise tolerance and QoL, by comparing the different phases separately.

MATERIALS AND METHODS

Data sources and search strategy

This study was designed according to the PRISMA statement (preferred reporting items for systematic reviews and meta-analyses).²⁸ We searched PubMed, EMBASE and the Cochrane Collaboration databases using the key words 'pulmonary hypertension', 'heart failure', 'sildenafil' and 'phosphodiesterase type-5 inhibitors' to identify RCTs and observational studies with a control group that evaluated the effects of sildenafil for PH-LHD. Our search included articles published from database inception until October 2014. The search was limited to English language articles. In addition, we manually searched references of retrieved articles, and we used PubMed's 'related articles' feature to identify studies not captured by our primary search design.

Study selection

We included nine RCTs and one observational trial with controls comparing the effectiveness response in PH-LHD patients treated with sildenafil versus placebo. The inclusion criteria were as follows: (1) receiving drug treatment and in a clinically stable condition (defined as no changes in HF regimens or hospitalization prior to study entry); (2) HFrEF; (3) included PH-LHD assessed by right heart catheterization or echocardiography; (4) negative exercise stress test; (5) no history of sildenafil intolerance, significant lung or valvular heart diseases, severe arrhythmia, neuromuscular disorders or peripheral vascular disease; (6) not taking long-acting nitrate preparations; (7) not receiving sildenafil at the time of study; and (8) no other pharmacotherapy with endothelin antagonists (bosentan, darusentan), prostanoids (epoprostenol, treprostinil, iloprost) or other PDE5 inhibitors (tadalafil). Studies were excluded if they were self-control studies. Reviews, editorials, letters, animal studies, case reports and conference abstracts were also excluded.

Data extraction

The literature search, data extraction and methodological grading were performed in duplicate by two independent reviewers (RJ, PY). Disagreements were resolved by consensus. We extracted data pertaining to the characteristics of all of the studies (number of subjects, type of trial, inclusion/exclusion criteria, length of follow-up, primary end points, results). The pooled efficacy outcomes noted were pulmonary hemodynamic measurements, cardio-pulmonary exercise testing (CPET) variables, systolic hemodynamic measures, left ventricle ejection fraction (LVEF) and QoL.

Outcomes

The primary outcome measurements were improvements in hemodynamic parameters and CPET after receiving sildenafil therapy versus placebo during the acute phase and over long-term follow-up. Secondary outcome measurements included improvements in LVEF and QoL between the acute phase and long-term follow-up.

Methodological quality

The risk of bias was assessed using domains suggested by the Cochrane Handbook of Systematic Reviews, specifically emphasizing sequence generation, allocation concealment, blinding, outcomes assessment and selective reporting for the nine RCTs (Supplementary Figure S1).²⁹ We used the Newcastle–Ottawa scale to assess the risk of bias for the observational studies (Supplementary Table S1).³⁰ Publication bias was assessed using Begg's adjusted rank correlation test (Supplementary Figure S2).

Data synthesis and statistical analysis

We conducted meta-analyses for comparisons when two or more studies reported the same outcome. Continuous variables were analyzed using weighted mean difference (WMD) or standardized mean differences. Throughout the article, values are presented as the mean $\pm$ s.d.s. unless otherwise stated. We used random-effect models or fixed-effect models to synthesize quantitatively the available evidence and to calculate summary estimates. For controlled studies, the difference in outcome measurement changes with sildenafil versus placebo was pooled across studies and was analyzed using a random-effect or fixed-effect model to compare heterogeneity using the I^2 statistic. Pooled analysis was calculated using fixed-effect models, and random-effect models were applied in cases of significant heterogeneity across studies. Separate models were constructed for the acute phase and at 3, 6 or 12 months of follow-up.

In our initial analysis, certain studies reported measurements of variability other than s.d. The only measurement of variability reported was the interquartile range. These cases, in which 95% confidence intervals or s.e.m. failed to convert to s.d., were excluded to maintain the consistency of the reported results. By including this study in the meta-analysis models, sensitivity analyses were performed. We considered $P < 0.05$ as significant.

The analysis was performed using the Stata software, version 12 (Stata, College Station, TX, USA), and RevMan software, version 5.1 (The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Characteristics of the studies

Of the 217 articles identified by the initial search, 112 articles were retrieved for more detailed evaluation, and 8 trials were included in the study (Figure 1). Ten studies were included in our systematic review, encompassing 299 patients treated between 2000 and 2013. The characteristics of all of the included studies are presented in Table 1. There were nine RCTs^{12–20} ($n = 286$) and one observational trial²⁷ with a control group ($n = 13$).

Pulmonary hemodynamic measurements

In five RCTs,^{14,16–18,20} sildenafil therapy decreased pulmonary artery systolic pressure (PASP) by -6.03 mm Hg (95% CI: -11.10 to -0.97 mm Hg, $P = 0.02$) and -11.47 mm Hg (95% CI: -14.70 to

Figure 1 Search flow diagram for studies included in the meta-analysis.

−8.24 mm Hg, $P < 0.00001$) at the acute phase and at the 6-month follow-up, respectively, in PH patients secondary to HFrEF, with significant heterogeneity between the studies ($I^2 = 96\%$ and 84% , respectively). Compared with placebo, sildenafil therapy was found to reduce mPAP (WMD: −3 mm Hg, 95% CI: −4.66 to −1.34 mm Hg, $P = 0.0004$), and pulmonary vascular resistance (PVR) (WMD: −60.0 dynes cm^{-5} , 95% CI: −105.51 to −14.49 dynes cm^{-5} , $P = 0.010$) at the 3-month follow-up. However, the pulmonary capillary wedge pressure (PCWP) remained unchanged (WMD: −1.0 mm Hg, $P = 0.13$) at the 3-month follow-up. No heterogeneity was observed in mPAP, PVR or PCWP (for all, $I^2 = 0$; Figures 2a–d).

Systematic hemodynamic measurements

In six of the included RCTs,^{12,13,16–19} sildenafil therapy did not influence resting systolic blood pressure (SBP), diastolic blood pressure (DBP) or heart rate (HR) regardless of acute phase or long-term follow-up.

Although sildenafil therapy increased HR (WMD: 2.89 beats per minute (b.p.m.), 95% CI: 0.85 to 4.93 b.p.m.) with no heterogeneity ($I^2 = 0$) at 3 months of follow-up. However, there were changes in HR of 0.63 b.p.m. (95% CI: −1.85 to 3.11 b.p.m., $P = 0.62$), 0.19 b.p.m. (95% CI: −3.13 to 3.52 b.p.m., $P = 0.91$) and 0.96 b.p.m. (95% CI: −0.64 to 2.56 b.p.m., $P = 0.24$) at the acute phase, the 6-month follow-up and overall, respectively (Figure 3a).

There were changes in SBP and DBP during the acute phase of −1.46 mm Hg (95% CI: −4.25 to 1.33 mm Hg) and −0.78 mm Hg (95% CI: −2.15 to 0.58 mm Hg) with sildenafil therapy versus placebo, respectively (for both $P > 0.05$). At 6 months, there were also reductions of 1.94 mm Hg in SBP (95% CI: −0.75 to 4.63 mm Hg) and 0.78 mm Hg (95% CI: −1.11 to 2.67 mm Hg), respectively. There was a modest amount of heterogeneity (all $I^2 = 0$ except $I^2 = 47\%$ during the acute phase for SBP; Figures 3b and c).

Cardiopulmonary exercise testing

The patients performed a progressively increasing work rate CPET to maximal tolerance on an electromagnetically braked cycle ergometer in the upright position. The oxygen consumption at peak exercise (peak VO_2), the efficiency of ventilatory response to carbon dioxide output (VE/ VCO_2 slope), oxygen consumption at the anaerobic threshold (AT) (VO_2 at AT), the ratio of dead space to tidal volume at peak exercise (peak VD/VT), peak respiratory exchange ratio (RER), peak workload and aerobic efficiency (the ratio of change in oxygen uptake to minute ventilation) ($\Delta\text{VO}_2/\Delta\text{WR}$) were evaluated to determine cardiopulmonary exercise capacity.

With regard to CPET, six RCTs^{13,14,16–19} and one observational study²⁷ were included to analyze peak VO_2 and VE/ VCO_2 slope.

There was no significant increase in peak VO_2 at acute duration (0.84 $\text{ml min}^{-1} \text{kg}^{-1}$, 95% CI: −0.38 to 2.07 $\text{ml min}^{-1} \text{kg}^{-1}$; $P = 0.18$, $I^2 = 80\%$). However, there were significant increases in peak VO_2 of 3.66 $\text{ml min}^{-1} \text{kg}^{-1}$ (95% CI: 2.74 to 4.57 $\text{ml min}^{-1} \text{kg}^{-1}$, $P < 0.00001$, $I^2 = 0\%$), 3.36 $\text{ml min}^{-1} \text{kg}^{-1}$ (95% CI: 2.46 to 4.27 $\text{ml min}^{-1} \text{kg}^{-1}$, $P < 0.00001$, $I^2 = 0\%$) and 2.60 $\text{ml min}^{-1} \text{kg}^{-1}$ (95% CI: 0.23 to 4.97 $\text{ml min}^{-1} \text{kg}^{-1}$, $P = 0.03$, $I^2 = 0\%$) at 3, 6 and 12 months, respectively, with sildenafil. Compared with placebo, there was an increase in peak VO_2 of 1.97 $\text{ml min}^{-1} \text{kg}^{-1}$ (95% CI: 0.76 to 3.17 $\text{ml min}^{-1} \text{kg}^{-1}$, $P = 0.002$, $I^2 = 79.4\%$) overall (Figure 4a).

There was no significant reduction in VE/ VCO_2 slope at the acute duration of −0.31 (95% CI: −2.89 to 2.27; $P = 0.81$). There were significant reductions in the VE/ VCO_2 slope of −2.00 (95% CI: −3.74 to −0.26, $P < 0.00001$, $I^2 = 0\%$), −4.68 (95% CI: −5.95 to −3.41, $P < 0.00001$, $I^2 = 0\%$) and −7.12 (95% CI: −8.83 to −5.41, $P < 0.00001$, $I^2 = 0\%$) at 3, 6 and 12 months, respectively. Compared with placebo, there was a reduction in VE/ VCO_2 slope of −2.70 (95% CI: −4.66 to −0.75) overall ($P = 0.007$, $I^2 = 87\%$). Compared with significant heterogeneity at the acute phase ($I^2 = 81\%$), there was no heterogeneity at 3, 6 or 12 months ($I^2 = 0\%$; Figure 4b).

Table 1 Characteristics and inclusion criteria of all included studies

Drug/ author	No. of patients	Design (type of the study)	Inclusion/exclusion criteria	Length of follow-up	Primary end point	Results
Bocchi <i>et al.</i> ¹⁹	<i>n</i> = 24 NYHA II–IV	Nearly 1:1 RCT dose of 50 mg	Standard criteria ^a no exception to HR < 55 b.p.m., high-risk arrhythmias, SBP < 85 mm Hg, low systemic perfusion, venous or pulmonary congestion; no female	Acute; 4 weeks	CPET variables; HR, SBP, DBP	HR, SBP, DBP and VE/VO ₂ ↓; peak VO ₂ ↑
Guazzi <i>et al.</i> ¹⁶	<i>n</i> = 24 NYHA II–III	2:1 RCT dose of 50 mg	Standard criteria ^a but no exception to hypertension, CoHb > 2%, no female	Acute	Hemodynamics; CPET; pulmonary function test	DLco, exercise peak VO ₂ , VE/VO ₂ slope aerobic (ΔVO ₂ /ΔWR)↑
Semigran, <i>et al.</i> ¹²	<i>n</i> = 34 NYHA II–IV	1:1 RCT dose of 25–50 mg tid	Standard criteria ^a with PH	12 weeks	CPET variables; hemodynamics; QoL	Peak VO ₂ , CO, 6MWT↑. No change in others
Semigran, <i>et al.</i> ²⁷	<i>n</i> = 13 NYHA III	Dose of 50 mg	Standard criteria ^a with LVEF < 35%	Acute	Exercise capacity; exercise hemodynamics	Decreased resting and exercise PAP, PVR, VE/VO ₂ slope; Increased resting and exercise CI, peak VO ₂
Clausell, <i>et al.</i> ²⁰	<i>n</i> = 19 NYHA I–III	1:1 RCT dose of 50 mg tid	Standard criteria ^a with clinically stable ≥ 2 months, except HR < 55 b.p.m., SBP < 90 mm Hg, atrial fibrillation, oral anticoagulation	Acute, 4-week duration	CPET variables; hemodynamics	Increased peak VO ₂ , SPAP, VE/VO ₂ slope. No change in others
Lewis <i>et al.</i> ¹³	<i>n</i> = 30 NYHA II–IV	1:1 RCT dose of 25–75 mg tid	Standard criteria ^a with PH	12 weeks	CPET variables; hemodynamics	VE/VO ₂ slope↓, positively associated with PVR, PCWP
Guazzi <i>et al.</i> ¹⁸	<i>n</i> = 32 NYHA II–III	1:1 randomi- zation dose of 50 mg	Chronic heart failure no exception to female	Acute	FMD; CPX variables	Decreased VE/VO ₂ slope, increased ΔVO ₂ /ΔWR, PAP, peak VO ₂ , LVEF
Guazzi <i>et al.</i> ¹⁷	<i>n</i> = 46 NYHA II–III	1:1 RCT dose of 50 mg tid	Standard criteria ^a no exception to SBP > 140 or < 110 mm Hg, diabetes mellitus, atrial fibrillation, no female	Acute; 3 and 6 months	CPET variables; hemodynamics; FMD	SPAP↓; peak VO ₂ , VE/VO ₂ slope, QoL↑
Guazzi <i>et al.</i> ^{11,14}	<i>n</i> = 45 NYHA II–III	2:1 RCT dose of 50 mg tid	Standard criteria ^a no exception to SBP < 110 mm Hg, LV assist devices.	Acute; 6 months 1 year	Hemodynamics; echocardiography; CPET; QoL; hormones	CPET variables↑, QoL↑, hor- mones↑; no change in others
Guazzi <i>et al.</i> ¹⁵	<i>n</i> = 32 NYHA III–IV	1:1 RCT doses of 50 mg tid	Standard criteria ^a with PH but no exception to SBP > 140 or < 110 mm Hg; no female	6 months, 1 year	Hemodynamics; CPET variables; QoL	Peak VO ₂ ↑, VE/VO ₂ slope↑; PCWP↓, mPAP↓, PVR↓; QoL↑

Abbreviations: BP, blood pressure; b.p.m., beats per minute; CHD, chronic heart disease; CI, cardiac index; CO, cardiac output; CoHb, carboxyhemoglobin; CPET, cardiopulmonary exercise testing; CPX, Cardiopulmonary Exercise Testing; DBP, diastolic blood pressure; DLco, lung diffusion for carbon monoxide; ED, erectile dysfunction; FEV1/FVC, forced expiratory volume 1 s/forced vital capacity ratio; FMD, flow-mediated brachial artery dilation; HF, heart failure; HR, heart rate; LV, left ventricular; LVAD, LV assist device; LVEDP, LV end-diastolic pressure; LVEF, LV ejection fraction; LVESF, LV end-systolic pressure; MAP, mean arterial pressure; mPAP, mean pulmonary arterial pressure; MRI, magnetic resonance imaging; NO, nitric oxide; NYHA, New York Heart Association functional class; PAWP, pulmonary artery wedge pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; QoL, quality of life; RCT, randomized controlled trial; SBP, systolic blood pressure; SPAP, systolic pulmonary arterial pressure; SVR, systemic vascular resistance; TPG, transpulmonary gradient; VE/VO₂ slope, slope of increase in ventilation versus carbon dioxide diffusion for carbon output; VO₂, oxygen consumption; 6MWT, 6-min walking distances; ΔVO₂/ΔWR, the ratio of change in oxygen uptake versus minute ventilation.

^aStandard criteria: these are the initial inclusion and exclusion criteria of chronic heart failure patients: stable chronic heart failure before the study, stable symptoms compatible with LVEF < 35 or 40 or 45% (required by different studies); no treatment with long-acting nitrate preparations; no history of intolerance of sildenafil and myocardial infarction, unstable angina, stroke, lung diseases with FEV1/FVC > 70%, valvular diseases, neuromuscular diseases; and not receiving sildenafil at the time of study.

There was a significant increase in VO₂ at an AT of 0.90 ml min⁻¹ kg⁻¹ (95% CI: -0.29 to 2.08 ml min⁻¹ kg⁻¹) at the acute duration (*I*² = 0%). The values of VO₂ at the AT increase were 2.61 ml min⁻¹ kg⁻¹ (95% CI: 0.86 to 4.36 ml min⁻¹ kg⁻¹) and 2.65 ml min⁻¹ kg⁻¹ (95% CI: 0.92 to 4.39 ml min⁻¹ kg⁻¹) at 6 and 12 months, respectively, with mild heterogeneity among studies (6-month follow-up, *I*² = 55%, *P* = 0.003; 12-month follow-up, *I*² = 22%, *P* = 0.003) in four RCTs^{14–17} compared with placebo. There was a significant increase in VO₂ at an AT of 2.01 ml min⁻¹ kg⁻¹ (95% CI: 1.03 to 2.99 ml min⁻¹ kg⁻¹) with mild heterogeneity overall (*P* < 0.0001, *I*² = 49.7%; Figure 4c).

There was no significant decrease in peak VD/VT of 0.01 (95% CI: -0.01 to 0.03) at the acute duration (*P* = 0.49, *I*² = 89%) in the four RCTs^{13,16,17,19} or one observational study²⁷ compared with placebo. The pooling analysis showed that additional sildenafil therapy significantly decreased peak VD/VT at the 3-month follow-up (WMD: -0.04, *P* < 0.00001; Figure 4d).

Left ventricle ejection fraction

There were no significant improvements in LVEF at the acute phase or 3-month follow-up (*I*² = 67, *P* = 0.74; *I*² = 50, *P* = 0.34, respectively) compared with placebo in four RCTs.^{13,14,16,17} However, sildenafil therapy was superior to placebo regarding LVEF at the 6-month follow-up with no heterogeneity (WMD: 4.35, 95% CI: 3.02 to 5.69, *I*² = 0, *P* < 0.00001; Figure 5).

Quality of life

QoL was assessed using a 16-question chronic HF questionnaire with answers scored from 1 (worse) to 7 (best).^{14,15,17} The QoL assessment documented a significant and sustained sildenafil-mediated improvement in breathlessness (WMD: 7.54 points, 95% CI: 5.75 to 9.34, *P* < 0.00001; WMD: 8.36 points, 95% CI: 5.86 to 10.86, *P* < 0.00001, respectively), fatigue (WMD: 3.20 points, 95% CI: -0.01 to 6.41, *P* = 0.05; WMD: 5.80 points, 95% CI: 2.92 to 8.68, *P* < 0.0001, respectively) and emotional function (WMD: 6.20 points, 95% CI:

Figure 2 Forest plots for pulmonary hemodynamic measurements. (a) Pulmonary arterial systolic pressure (PASP) at 3-month follow-up. (b) Mean pulmonary artery pressure (mPAP) at 3-month follow-up. (c) Pulmonary vascular resistance (PVR) at 3-month follow-up. (d) Pulmonary capillary wedge pressure (PCWP) at 3-month follow-up. CI, confidence interval; IV, inverse variance.

3.71 to 8.70, $P < 0.00001$; WMD: 4.57 points, 95% CI: 1.53 to 7.62, $P < 0.003$, respectively) at the 6- and 12-month follow-ups, respectively. There was no significant heterogeneity among these studies (both breathlessness and emotional function, $I^2 = 0\%$; fatigue, $I^2 = 50\%$, overall; Figures 6a–c).

DISCUSSION

The present study demonstrated that PDE5 inhibitors (sildenafil) can be helpful in PH-LHD with HFrEF. Based on standard chronic HF therapy, additional sildenafil treatment significantly improves PASP regardless of whether as a short- or long-term treatment. Chronic therapy can improve mPAP and QoL in PH-LHD with HFrEF. Although there were no significant improvements in LVEF at the acute phase or at 3 months of follow-up, sildenafil therapy was superior to placebo regarding LVEF at the 6-month follow-up with no heterogeneity. There were significant improvements in peak VO_2 , VE/VCO_2 slope, VO_2 at AT and peak VD/VT during chronic therapy only.

In our study, sildenafil significantly reduced the PASP, mPAP and PVR levels, although the PCWP level remained unchanged. We could not verify whether there were significant improvement in CO or cardiac index due to a lack of sufficient data to evaluate the effects.^{15,27} Sildenafil-lowering PAP and PVR in our study was consistent with the findings of Huang *et al.*²⁶ However, our research showed that sildenafil not only reduced PASP within 1–2 h after administration but also generates more obvious effect at 6 months of follow-up in patients with HFrEF, different from Huang *et al.*,²⁶ who studied the chronic effect of sildenafil on mPAP and PVR by mixing different follow-up lengths. We believe that the chronic effects of sildenafil should be analyzed stepwise by subgroup meta-analysis according to follow-up time because the long-term effects of the drug might be different at different times. We evaluated only changes in mPAP and PVR at 3 months of follow-up due to a lack of sufficient data to evaluate the effects at 6 or 12 months.

Figure 3 Forest plots for pulmonary systematic hemodynamic measurements. (a) Heart rate (HR). (b) Systolic blood pressure (SBP). (c) Diastolic blood pressure (DBP). CI, confidence interval; IV, inverse variance.

Systemic BP in PH patients tends to be low. In this meta-analysis, sildenafil produced a selective response in the pulmonary vessels without significant changes in the left heart hemodynamic variables, not only in the acute phase but also in the chronic phase. The study by

Bocchi *et al.*¹⁹ showed that sildenafil treatment did not result in a greater reduction in systemic BP or in patients receiving nitrates for pulmonary congestion. Sildenafil therapy also had no effect on HR.

Figure 4 Forest plots for cardiopulmonary exercise testing. (a) Oxygen consumption at peak exercise (peak VO₂). (b) The efficiency of ventilatory response to carbon dioxide output (VE/VCO₂ slope). (c) VO₂ at anaerobic threshold (AT) (VO₂ at AT). (d) The ratio of dead space to tidal volume at peak exercise (peak VD/VT). CI, confidence interval; IV, inverse variance.

Figure 4 continued

Figure 5 Forest plots for left ventricle ejection fraction. CI, confidence interval; IV, inverse variance.

Figure 6 Forest plots for quality of life. (a) Breathlessness. (b) Fatigue. (c) Emotional function. CI, confidence interval; IV, inverse variance.

Our meta-analysis showed that one-time or chronic administration of sildenafil to patients with HFrEF improved peak VO_2 , VO_2 at AT and reduced VE/VCO_2 slope (Figures 4a–c). The changes in peak VO_2 , VO_2 at AT or VE/VCO_2 slope at 3, 6 and 12 months were all consistent. Exercise capacity, as measured by peak VO_2 , is a well-established independent predictor of prognosis in patients with advanced systolic HF.^{31–33} The improvement in peak VO_2 observed with sildenafil treatment in this study was attributable to augmentation of CO. Several mechanisms could account for this improvement in CO. Sildenafil improved RV systolic function, as

reflected by an increase in RVEF, measured with radionuclide ventriculography.¹²

The correlation between the changes in peak VO_2 with sildenafil treatment and baseline PAP also suggests that a reduction in RV afterload might have mediated the improvement in exercise capacity. This augmentation in RV function was likely attributable to afterload reduction because sildenafil reduces PVR.²⁷

An exaggerated ventilatory response to exertion is perceived as a sense of breathlessness and is objectified by an increase in VE/VCO_2 slope. Hyperventilation can help in maintaining the normal alveolar

tension of oxygen, which, however, accelerates exhaustion of the ventilatory reserve and an interruption of exercise. Several mechanisms could explain the basis of hyperventilation, that is, hypoperfusion of the lungs, enlarged dead space of the lungs, bicarbonate buffering of accumulated lactic acid, pulmonary interstitial space distension and abnormal drive from the reflexogenic areas of the cardiovascular system,³⁴ skeletal muscle over-signaling and increased passage of fluid from the lungs intravascularly to the interstitial phase because of an excessive increase of the pulmonary capillary pressure on exertion.¹⁸ It is inferable that an improvement in exercise pulmonary hemodynamics, CO and peripheral perfusion could attenuate many of these disorders, augmenting exercise capacity and reducing hyperventilation.

Chronically elevated resting left-sided filling pressures might contribute to inadequate pulmonary vasodilation and high VD/VT.¹³ Inefficient ventilation in patients with advanced HF has been ascribed to abnormalities in gas exchange (higher VD/VT), as well as to an independent, 'primary' drive to hyperventilation that results in low PaCO₂.³⁵ Lewis *et al.*¹³ observed both a positive correlation between PVR and VD/VT at peak exercise and a negative correlation between PVR and arterial PaCO₂ at peak exercise. Peak VD/VT had a positive correlation with PVR. In our study, although peak VD/VT remained unchanged at the acute phase, peak VD/VT was significantly reduced at 3 months of follow-up.

Some studies have reported that sildenafil intake was associated with increases in peak RER,^{16,27} peak workload¹⁶ and $\Delta\text{VO}_2/\Delta\text{WR}$;^{16,18} however, we noted that sildenafil did not produce significant changes in peak RER, peak workload or $\Delta\text{VO}_2/\Delta\text{WR}$ (Supplementary Figures 3A–C).

Some studies in animals and humans with HF have indicated that PDE5 inhibition does not alter myocardial contractility.^{36–38} Nagendran *et al.*³⁸ suggested that PDE5 inhibition could increase RV contractility in the setting of RV hypertrophy. In the study by Huang *et al.*,²⁶ additional sildenafil intervention enhanced LV function in HFrEF patients with long-term treatment of sildenafil. However, in our meta-analysis, we revealed that sildenafil improved LVEF at 6 months of chronic therapy. One-time or 3-month administration of sildenafil did not improve LVEF (Figure 5). We conclude that LVEF, as measured by echocardiography, might require a longer time to show significant change.

Sildenafil has been shown to be effective as a pulmonary vasodilator through selective inhibition of PDE5 in patients with pulmonary pressure increases secondary to chronic HF. These effects are explainable on the basis of the mechanism of action of the drug. Sildenafil, by slowing the degradation of cGMP, potentiates the effects of limited nitric oxide production in the presence of endothelial dysfunction, particularly in HF.³⁹ Reductions in PAP and PVR lead to improved LVEF, increased CO, enhanced exercise performance²⁷ and a shortened diffusion path between the alveoli and capillaries because of diminished fluid flux transition into the alveolar interstitial space.¹⁶

The QoL assessment documented a significant and sustained sildenafil-mediated improvement in breathlessness, fatigue and emotional function.

Limitations

First, the number of studies was limited. Second, all of the included studies had small sample sizes, were single-center studies; multicenter clinical trials with larger sample size in PH-LHD with HFrEF are currently under way, including Sildenafil in Heart Failure,⁴⁰ and they might address these issues. Third, the included population had different characteristics, such as the patient's age, sex, treatment history and so on. The population with HF is more heterogeneous

than in PAH, resulting in complex polypharmacy. Patients should be defined in future large-scale clinical trials. Fourth, the longest follow-up duration was only 12 months. We expect longer observation times in future studies. Finally, although encouraging, the results should be treated with caution because the studies were single-center studies and used a range of doses of sildenafil (from 25 to 75 mg tid) that were consistently higher than the doses approved to treat PAH.

CONCLUSIONS

The present meta-analysis suggested that sildenafil improved pulmonary hemodynamics, both at the acute phase and over long-term follow-up, without changes in HR or systematic blood pressure. Sildenafil therapy also improves CPET measurements, LVEF and QoL, during both the acute phase and over long-term follow-up. Although it might be challenging, carefully controlled trials with larger and subset populations, ideally in similar proof concept and phase III studies (that is, identified by invasive hemodynamic status, performed in the same clinical setting with patients on optimized and stable therapy), are needed. These studies will show the exact effects of sildenafil in such a patient group.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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